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Longitudinal Association of Glucose Metabolism With Retinopathy

Results from the Australian Diabetes Obesity and Lifestyle (AusDiab) study

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OBJECTIVE — We determined the longitudinal association of glucose metabolism with retinopathy in a sample of the Australian population.

RESEARCH DESIGN AND METHODS — The Australian Diabetes Obesity and Lifestyle (AusDiab) study is a national, longitudinal study of adults aged ≥25 years from 42 randomly selected areas of Australia. Retinopathy was assessed at baseline in 1999–2000 and 5 years later in 2004–2005 in participants identified as having diabetes (based on self-report and oral glucose tolerance test) and impaired glucose metabolism and in a random sample with normal glucose tolerance. Complete retinal data were available for 1,192 participants. Photographs were graded at two time points according to a simplified version of the Wisconsin grading system.

RESULTS — The 5-year incidences of retinopathy were 13.9 and 3.0% among those with known and newly diagnosed diabetes at baseline, respectively. Of those who developed incident newly diagnosed diabetes at follow-up, 11.9% had retinopathy at baseline compared with 5.6% of those who did not progress to incident newly diagnosed diabetes ($P = 0.037$). After adjustment for factors identified as risk factors for diabetes, individuals with retinopathy signs at baseline were twice as likely to develop incident newly diagnosed diabetes compared with those who did not have retinopathy signs at baseline.

CONCLUSIONS — The 5-year incidence of retinopathy was 13.9% among individuals with known diabetes. Nondiabetic individuals with retinopathy signs at baseline had a twofold higher risk of developing incident newly diagnosed diabetes 5 years later. This result provides further evidence that mild retinopathy signs may be a preclinical marker of underlying microvascular disease and future diabetes risk.

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Diabetic retinopathy is a common complication of diabetes and remains a leading cause of visual loss throughout the world, despite the availability of effective health care interventions. Although the epidemiology of retinopathy has been extensively studied, there are few national population-based studies on the incidence and risk factors for diabetic retinopathy, and only a limited number have assessed the development of retinopathy across the spectrum of glucose values from normal glucose tolerance to the diabetic range (1,2).

Contemporary data on the incidence of retinopathy in individuals with different levels of abnormal glucose metabolism is important in determining the relative contribution of glycemia to the development of retinopathy. There is now increasing evidence that retinopathy signs typical of diabetes are in fact present in up to 10% of those with normal glucose tolerance (3). In individuals with and without diabetes, these signs have been associated with an increased risk of stroke (4), congestive heart failure (5), cardiovascular disease, and mortality (6) and the subsequent development of diabetes (7), independent of other well-established risk factors. We now report on the 5-year incidence and risk factors for retinopathy across categories of glucose metabolism and the association of retinopathy signs detected at baseline with subsequent development of diabetes.

RESEARCH DESIGN AND METHODS

— The population, methods, and response rates of Australian Diabetes Obesity and Lifestyle (AusDiab) study are discussed in detail elsewhere (8). In brief, the AusDiab study was a population-based study of 11,247 people aged ≥25 years, from 42 randomly selected urban and rural areas of Australia, conducted in 1999–2000. The response rate for the baseline survey was 55.3% ($n = 11,247$), and the follow-up response rate in 2004–2005 was 60.6% (6,537/10788); 459 individuals were ineligible for the follow-up study because of a terminal illness or death or because they refused further contact.

The study was approved by the ethics committee of the International Diabetes Institute. Informed consent for the study was obtained from all participants.

At baseline, people identified through the AusDiab study as having diabetes (known and newly diagnosed by oral glucose tolerance test in the survey), impaired glucose metabolism (defined by impaired fasting glucose or impaired glucose tolerance), and a random sample of people with normal glucose tolerance (NGT) were invited to participate in the baseline complications survey. Of 2,773 participants invited for the complications component, 2,476 attended at baseline (overall response rate 89%, 91% in those with diabetes and 88% in those without diabetes). Of the 2,476 participants in this substudy, we excluded 1,126

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Table 1—*Five-year incidence of retinopathy by baseline glucose tolerance status and age-group: the AusDiab study*

		Retinopathy incidence in age-group			
Glucose tolerance status	*n*	≥25 years	25–44 years	45–64 years	≥65 years
NGT at baseline	227	1.8	1.2	3.0	0
IFG/IGT at baseline	557	0.7	0.0	1.0	0.6
NDM at baseline	168	3.0	0.0	2.0	5.9
KDM at baseline	144	13.9	0.0	15.2	14.0

Data are numbers and percentages (%). IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NDM, newly diagnosed diabetes; KDM, known diagnosed diabetes.

(45.5%) who did not attend the 5-year follow-up examination and 158 (6.4%) who had ungradable photographs at either baseline or follow-up, leaving 1,192 participants for this analysis (see Fig. 1 of an online appendix, available at http://dx.doi.org/10.2337/dc07-1707). Compared with nonresponders, responders included in the analysis were younger (mean age 56 vs. 61 years, $P < 0.001$), were less likely to smoke (10 vs. 15%, $P < 0.001$), had a slightly lower prevalence of retinopathy (8 vs. 11%, $P = 0.016$), and had lower A1C (5.7 vs. 5.8%, $P = 0.004$) at baseline. There were no baseline differences in the percentage of men (49 vs. 51%, $P = 0.505$), the percentage of those with hypertension (52 vs. 56%, $P = 0.123$), mean total cholesterol (5.7 vs. 5.6mmol/l, $P = 0.241$), or duration of diabetes among those with known diagnosed diabetes (8.5 vs. 8.2 years, $P = 0.593$).

Diabetes classification was based on plasma glucose results, using the 1999 World Health Organization diabetes classification (9). Incident newly diagnosed diabetes at 5 years was defined as an individual without known diagnosed diabetes or newly diagnosed diabetes at baseline in whom diabetes was diagnosed at the follow-up examination. Incident known diagnosed diabetes at 5 years was defined as an individual without known diagnosed diabetes or newly diagnosed diabetes at baseline in whom diabetes was diagnosed between baseline and follow-up by the individual's physician.

Assessment of retinopathy

Retinal photographs were taken at baseline and at follow-up with a nonmydriatic retinal camera (Canon CR6-45NM). At the baseline examination, the camera had an adapter fitted with a Sony three-chip charge-coupled device. However, this camera was updated to a digital camera backing for the follow-up visit in 2004–2005, resulting in higher resolution and quality of digital images. Two photographic fields, one centered on the optic disc and the second on the macula, were taken of each eye after dark adaptation without the use of dilating drops. One assessor, masked to all participant information, graded the photographs at baseline and follow-up. Level of retinopathy was defined according to a simplified version of the Wisconsin grading system (10), with the classification of an individual being based on the grading of the worst eye. A random sample of 167 retinal photographs at baseline (with and without retinopathy) were regraded (by the same assessor) to assess the internal validity of the grading. Overall there was a high degree of agreement between the first and second grading of retinopathy ($\kappa = 0.732$, unweighted).

To identify participants with incident retinopathy, we selected images from all participants with any retinopathy at follow-up (as determined from retinal images) and then verified the absence of any retinopathy lesions in the baseline images. Incident retinopathy was defined as the presence of retinal microaneurysm and/or hemorrhage at the 5-year follow-up. All cases of incident retinopathy were adjudicated by a retinal specialist.

Other measurements

In 1999–2000, fasting plasma glucose (FPG) and 2-h plasma glucose levels were determined by a glucose oxidase method using an Olympus AU600 automated analyzer (Olympus Optical, Tokyo, Japan), and in 2004–2005, a spectrophotometric-hexokinase method with a Roche Modular system (Roche Diagnostics, Indianapolis, IN) was used. Details on the assays used in the studies can be found in detail elsewhere (8). Urinary albumin and creatinine were also determined in a spot morning urine specimen by enzymatic methods (Olympus AU600 analyzer). Serum triglycerides, total cholesterol, and HDL cholesterol were measured by similar enzymatic methods at baseline. For total A1C analysis, high-performance liquid chromatography (Bio-Rad Variant Hemoglobin Testing System; Bio-Rad, Hercules, CA) with standardized conversion to A1C values (normal range 4.2–6.3%) was used. C-peptide was measured by radioimmunoassay with human C-peptide kits (Linco Research, St. Charles, MO). Blood pressure was measured using a Dinamap monitor or a standard mercury sphygmomanometer. To account for any effect of differential measurement error, blood pressure measurements were adjusted as described previously (11). Hypertension was defined as being present if systolic blood pressure was ≥140 mmHg, if diastolic blood pressure was ≥90 mmHg, or if the participant reported current treatment for hypertension. Height and weight were measured in light clothing by a trained observer. BMI was calculated as weight in kilograms divided by the square of height in meters. Information on smoking, medications, and history of diabetes were obtained by interview.

Statistical methods

Data analysis was performed with SPSS (version 14.0.0 for Windows; SPSS, Chicago, IL). Descriptive information for each of the variables was derived, and distribution was assessed. Logistic regression modeling was used to assess risk factors for incident retinopathy among those with diabetes. Only factors identified to be significantly associated with incident retinopathy at model 2 were include in the multivariate model (model 3). Logistic regression was also used to determine the association of baseline retinopathy with incident diabetes.

RESULTS

Incident retinopathy

The 5-year incidence of retinopathy by glucose metabolism is shown in Table 1. The incidences of mild, moderate, and severe nonproliferative diabetic retinopathy (NPDR) among those with known diabetes were 9.7, 2.8, and 0.7%, respectively. Proliferative diabetic retinopathy (PDR) developed in 0.7%. Among those with newly diagnosed diabetes at baseline, no incident cases of PDR were identified. Of those with known diabetes and mild

Table 2—*Characteristics of the population at baseline (diabetes only)*

	No retinopathy	Incident retinopathy	*P* value
n	287	25	
Age (years)	60 ± 11	63 ± 10	0.175
Male sex (%)	53	60	0.499
FPG (mmol/l)	7.6 ± 1.9	10.8 ± 3.8	<0.001
2-h plasma glucose (mmol/l)*	12.4 ± 3.6	16.2 ± 6.9	0.006
A1C (%)	6.3 ± 1.2	8.5 ± 1.9	<0.001
C-peptide (ng/ml)	3.9 ± 1.7	2.9 ± 1.8	0.007
Known diabetes (%)	43	80	0.001
Duration of diabetes (years)†	0 (0–3)	5 (2–9)	<0.001
Taking insulin or tablets (%)	57	90	0.007
BMI (kg/m²)	30.4 ± 5.9	29.1 ± 6.1	0.296
Waist circumference (cm)	101.4 ± 13.7	98.8 ± 12.9	0.366
Albumin-to-creatinine ratio (mg/mmol)	0.8 (0.5–1.6)	1.2 (0.5–4.5)	0.115
Lipid treatment (%)	26	28	0.001
HDL cholesterol (mmol/l)	1.2 ± 0.3	1.2 ± 0.4	0.971
Total cholesterol (mmol/l)	5.7 ± 1.0	5.2 ± 0.9	0.026
Triglycerides (mmol/l)	1.9 (1.3–2.8)	1.7 (0.8–2.6)	0.189
Current smoker (%)	10	4	0.334
Hypertension (%)	40	40	0.313
SBP (mmHg)	142 ± 18	152 ± 23	0.005
DBP (mmHg)	75 ± 12	78 ± 14	0.334

Data are means ± SD or median (interquartile range). *Those with KDM and on current treatment with tablets or insulin did not undergo an oral glucose tolerance test. †Newly diagnosed participants given duration of zero. DBP, diastolic blood pressure; SBP, systolic blood pressure.

NPDR at baseline, 50% at follow-up had no evidence of retinopathy and 17.6% had progressed, including 2.9% who had developed PDR. Four of the five participants with evidence of retinopathy at baseline and PDR at follow-up had undergone laser treatment. Of those with known diabetes and incident retinopathy, 76% failed to meet the target for glycemic control of ≤7% (12) and 88% failed to meet targets for blood pressure control of <130/85 mmHg (13). Incident macular edema occurred in 4.8% of participants with known diabetes, and this was bilateral in four participants. Five of the eight participants with incident macular edema had undergone laser treatment.

Among those with diabetes, factors significantly associated with incident retinopathy in univariate analysis are shown in Table 2. Logistic regression identified systolic blood pressure, FPG, and C-peptide as independent factors associated with incident retinopathy (after adjustment for age and BMI) (Table 3). Replacing FPG in the model with A1C improved the strength of the retinopathy association with hyperglycemia (odds ratio [OR] for A1C 2.32; $P < 0.001$). However, the association with age and BMI were attenuated (data not shown).

Baseline retinopathy and incident diabetes

Of those who developed incident newly diagnosed diabetes at follow-up, 11.9% had retinopathy at baseline compared with 5.6% of those who did not progress to incident newly diagnosed diabetes ($P = 0.037$). Among those with incident known diabetes identified in between examinations ($n = 0$), none had retinopathy signs at baseline. Those with evidence of retinopathy present at baseline who later progressed to incident newly diagnosed diabetes all had NPDR at baseline. After adjustment for factors identified in univariate analysis (Table 4, model 1) as risk factors for diabetes (FPG, triglycerides, and waist circumference), participants with retinopathy signs at baseline were twice as likely to develop incident newly diagnosed diabetes compared with those who did not have retinopathy signs at baseline (OR 2.66 [95% CI 1.14–6.21]).

CONCLUSIONS — There were two principal findings in this population-based prospective study in Australia. First, we report on the 5-year incidence of retinopathy among individuals in different categories of glycemia. Our study is one of a few national studies assessing retinopathy signs across the spectrum of hyperglycemia and impaired glucose metabolism as defined by an oral glucose tolerance test. We found a relatively low 5-year incidence of retinopathy across categories of glucose metabolism. Second, we report on the longitudinal rela-

Table 3—*ORs (95% CI) of risk factors for incident retinopathy among those with diabetes at baseline*

	Incident retinopathy
Model 1: adjusted for age (years)	1.03 (0.98–1.07)
Model 2: one by one adjustment	
Model 1 and sex	0.72 (0.31–1.67)
Model 1 and BMI (kg/m²)	0.97 (0.99–1.05)
Model 1 and SBP (mmHg)	1.03 (1.01–1.06)
Model 1 and total cholesterol (mmol/l)	0.80 (0.23–2.80)
Model 1 and FPG (mmol/l)	1.52 (1.30–1.77)
Model 1 and A1C (%)	2.29 (1.75–3.02)
Model 1 and PLG (mmol/l)	1.24 (1.07–1.45)
Model 1 and C-peptide (ng/ml)	0.69 (0.53–0.91)
Model 1 and duration of diabetes (years)	1.06 (1.02–1.12)
Model 1 and smoking	1.61 (0.69–3.75)
Model 3: multivariate adjustment for	
C-peptide (ng/ml)	0.56 (0.38–0.83)
FPG (mmol/l)	1.56 (1.32–1.85)
BMI (kg/m²)	1.03 (0.93–1.14)
SBP (mmHg)	1.04 (1.02–1.07)
Age (years)	1.04 (0.99–1.09)

Model 1: OR for retinopathy by age. Model 2: OR for incident retinopathy for each factor (sex, BMI, systolic blood pressure [SBP], total cholesterol, FPG, A1C, PLG, C-peptide, duration of diabetes, and smoking) adjusted for age. Model 3: OR of incident retinopathy for C-peptide, FPG, BMI, SBP, and age (adjusted for each other). PGL, postload glucose.

Table 4—*ORs (95% CI) for retinopathy as a risk factor for incident newly diagnosed diabetes (those with diabetes at baseline excluded)*

	Incident diabetes
Model 1: One by one adjustment:	
Baseline retinopathy	2.37 (1.06–5.28)
FPG (mmol/l)	3.05 (1.91–4.87)
SBP (mmHg)	1.01 (0.99–1.02)
Total cholesterol (mmol/l)	1.16 (0.90–1.49)
Triglycerides (mmol/l)	2.21 (1.43–3.41)
Waist circumference (cm)	1.04 (1.02–1.06)
Age (years)	1.01 (0.99–1.03)
Sex	0.75 (0.45–1.24)
Current smoking	1.41 (0.65–3.09)
Model 2: adjusted for age and sex	
Baseline retinopathy	2.31 (1.03–5.16)
FPG (mmol/l)	3.05 (1.86–4.98)
Triglycerides (mmol/l)	2.14 (1.38–3.32)
Waist circumference (cm)	1.04 (1.01–1.06)
Model 3: multivariate adjustment for	
Baseline retinopathy	2.66 (1.14–6.21)
FPG (mmol/l)	2.56 (1.54–4.24)
Triglycerides (mmol/l)	1.82 (1.13–2.93)
Waist circumference (cm)	1.01 (0.99–1.04)

Model 1: univariate association of baseline retinopathy, FPG, triglycerides, waist circumference, age, sex, and smoking with incident diabetes. Model 2: association of retinopathy, FPG, triglycerides and waist circumference with incident diabetes (adjusted for age and sex). Model 3: association of baseline retinopathy, FPG, triglycerides, and waist circumference with incident diabetes (adjusted for each other). SBP, systolic blood pressure.

tionship of baseline retinopathy with incidence of diabetes. We showed that nondiabetic individuals with retinopathy signs at baseline had a twofold higher risk of developing incident newly diagnosed diabetes 5 years later.

Our study should be compared with the few other prospective studies available. The 5-year incidence of retinopathy among those with known diabetes was similar to the 5-year incidence observed in the Melbourne Visual Impairment study (11%) and the 9-year incidence observed in the Hoorn study (17.5%) (1,14). However, these estimates are considerably lower than those observed in the majority of previous population-based studies (15,16). In the Barbados Eye Study of adults aged 40–84 years, the 4-year incidence of diabetic retinopathy was 32%; in the Blue Mountains Eye Study of adults aged ≥49 years, the 5-year incidence was 22%; and in the San Luis Valley eye study the 4-year incidence was 23% (15,16). There are several possible reasons for this difference in incidence. First, there are differences in diabetes duration and glycemic control among studies. The participants in the AusDiab study had a relatively short duration of diabetes. We showed that retinopathy incidence was highest (34%) among participants with the longest duration of diabetes (>8 years) and worst glycemic control (A1C >6.7%) compared with just 1% among those with shorter diabetes duration and lower levels of A1C. Second, differences in frequency of other risk factors (e.g., hypertension) may also partly explain difference in incidence across studies. Finally, differing methods for ascertaining retinopathy would have an impact on the reported incidence (16–18).

In the current study, 17.6% of those with mild NPDR at baseline (known diabetes and newly diagnosed diabetes) had progressed to moderate NPDR (14.7%) or PDR (2.9%) by follow-up. Of those with moderate NPDR at baseline, 50% (known diabetes and newly diagnosed diabetes) had moderate NPDR at follow-up and 50% had regressed to mild NPDR. Previous research has shown that those with moderate NPDR are more likely to progress to PDR than show signs of regression (19). This finding, along with the improvement among those with mild NPDR (in 50% of patients), suggests that part of this population may be well treated. Regression of mild NPDR has been observed previously (14,18,19) and is possibly related to improved metabolic control and blood pressure.

The 5-year incidence of retinopathy among those with NGT and impaired glucose metabolism at baseline was also relatively low in contrast to that in other studies (1,2,18,20). In the Hoorn study, which determined the 9-year incidence of retinopathy among individuals aged 50–74 years, the incidence of retinopathy was 7% among those with NGT and 14% among those with impaired glucose metabolism (1). In the Atherosclerosis Risk in Communities Study, the 3-year incidence of retinopathy among those without diabetes was 2.9%, and the incidence increased with age from 2% among those aged 50–54 years to 5.2% among those aged 65–73 years (18). The Blue Mountains Eye Study reported a 5-year incidence of 9.7% among those aged ≥49 years (2), and the Beaver Dam Eye Study reported an incidence of 6% among those aged 55–74 years (20). The strong association between age and retinopathy may partly explain the difference in incidence of retinopathy among those without diabetes across different studies. Other factors, including the presence of hypertension and differing methods for ascertaining retinopathy, would also have an impact on the reported incidence.

Independent risk factors for retinopathy among those with diabetes (both previously and newly diagnosed diabetes at baseline) were C-peptide, FPG, and blood pressure. Both FPG and blood pressure are known for their strong association with diabetic retinopathy. The Hoorn study showed that those with retinopathy had higher glycemic values and were hypertensive (1); a similar finding was shown in the Atherosclerosis Risk in Communities study (18). The UK Prospective Diabetes Study (UKPDS), a clinical trial of 4,585 people with type 2 diabetes, showed that intensive glycemic and blood pressure control significantly reduced the incidence and progression of retinopathy and visual loss (21). The study additionally showed that intensive treatment of both risk factors had an additive effect (22). In the present study 76% of participants with incident retinopathy failed to meet the target for glycemic control of ≤7% (12) and 88% failed to meet targets for blood pressure control of <130/85 mmHg (13). More aggressive management of modifiable risk factors could reduce the numbers of individuals who develop retinopathy.

Our second principal finding was the

demonstration of a twofold risk of development of incident newly diagnosed diabetes among nondiabetic individuals with retinopathy signs at baseline. We should emphasize that the majority of those with retinopathy at baseline did not go on to develop incident newly diagnosed diabetes (only 8 of 67 participants progressed). No cases of retinopathy were identified among those with incident known diabetes. However, the association of retinopathy with incident newly diagnosed diabetes was significant and similar to the strength of the association of FPG with incident diabetes (Table 4). This association is consistent with results from the Beaver Dam Eye Study (23), the Atherosclerosis in Communities study (7), and the Blue Mountains Eye Study (24). The Beaver Dam Eye Study showed that retinopathy among those without diabetes at baseline was associated with the 15-year incidence of diabetes (among those aged <65 years) (23). The Blue Mountains Eye Study, which reexamined 2,335 adults aged ≥49 years, showed that among those with retinopathy and free of diabetes at baseline, the incidence of diabetes was 3.5% (24). The authors highlighted the fact that for the majority of participants, in those without diabetes, there was no association of vascular retinopathy signs with blood glucose and suggested that the association was likely to have many etiologies, with older age and blood pressure being the major contributing factors. Further research is needed in this area to clarify the importance of retinopathy in relation to the incidence of diabetes.

The present study has several limitations. Duration of diabetes was based on self-report, without confirmation from medical records. Age, A1C, and slight difference in the prevalence of retinopathy between responders and nonresponders probably caused a slight underestimation of the incidence. A relatively small number of individuals with retinopathy were identified in this study. Therefore, only factors very strongly associated with incident retinopathy and diabetes were detectable. A longer follow-up time may see additional associations identified, including microalbuminuria, which at this point was not shown to be associated with incident retinopathy. No measures of genetic factors were assessed in this study. Genetic differences between populations may be a strong governing factor in the development and progression of retinopathy.

In summary, we report the 5-year incidence of retinopathy in a national population-based cohort study. The present study showed that the incidence of retinopathy in Australia is relatively low compared with that seen in older studies. We identified a twofold risk of development of incident newly diagnosed diabetes among participants without diabetes who had retinopathy at baseline. This result suggests that mild background retinopathy may be a preclinical marker of microvascular disease and future diabetes risk and may identify a particular high-risk group for possible early intervention. This suggestion clearly warrants further investigation.

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